Targeted mutation of the mouse Grp94 gene disrupts development and perturbs endoplasmic reticulum stress signaling.

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Public Summary:
Glucose-regulated protein, 94 kDa, GRP94, is an abundant chaperone in the endoplasmic reticulum (ER) that helps protein processing and regulates ER homeostasis. However, beyond its chaperoning function, it is also implicated in cancer progression and autoimmune disease. To understand the physiological role of GRP94, we created mice with genetic deletion of one or two copies of GRP94. While single deletion of GRP94 did not alter cellular response to ER stress, double deletion of GRP94 led to compensatory upregulation of other ER chaperones. Unexpectedly, deletion of GRP94 suppressed the downstream of IRE1 (inositol-requiring enzyme 1) pathway upon ER stress. From our microarray database, we were able to predict which organs GRP94 may play an important role in.

Scientific Abstract:
Glucose-regulated protein 94 (GRP94) is one of the most abundant endoplasmic reticulum (ER) resident proteins and is the ER counterpart of the cytoplasmic heat shock protein 90 (HSP90). GRP94, a component of the GRP78 chaperone system in protein processing, has pro-survival properties with implicated function in cancer progression and autoimmune disease. Previous studies on the loss of GRP94 function showed that it is required for embryonic development, regulation of toll-like receptors and innate immunity of macrophages. Here we report the creation of mouse models targeting exon 2 of the Grp94 allele that allows both traditional and conditional knockout (KO) of Grp94. In this study, we utilized the viable Grp94+/+ and +/- mice, as well as primary mouse embryonic fibroblasts generated from them as experimental tools to study its role in ER chaperone balance and ER stress signaling. Our studies reveal that while Grp94 heterozygosity reduces GRP94 level it does not alter ER chaperone levels or the ER stress response. To study the effect of complete loss of GRP94 function, since homozygous GRP94 KO leads to embryonic lethality, we generated Grp94-/- embryonic stem cells. In contrast to Grp94 heterozygosity, complete knockout of GRP94 leads to compensatory upregulation of the ER chaperones GRP78, calnexin and calreticulin but not protein disulphide isomerase. Unexpectedly, loss of GRP94 leads to significant decrease in the level of ER-stress induced spliced form of XBP-1 protein, a downstream target of the IRE1 signaling pathway. Furthermore, from analysis of microarray database and immunohistochemical staining, we present predictions where GRP94 may play an important role in specific adult organ homeostasis and function.